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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,302	08/01/2003	Chester Li	5026CON	5848

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,302	LI ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *2-10,12,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application has been transferred to examiner Quang Nguyen, Ph.D. in GAU 1633.

Claims 1-15 are pending in the present application.

Applicant's election of the following species without traverse in the reply filed on 2/6/06 is acknowledged. The elected species are: (a) hemophilia B is a species of a systemic disorder or disease, and (b) Factor VIII as a species of a therapeutic protein.

Accordingly, claims 2-10, 12 and 14-15 are withdrawn from further consideration because they are directed non-elected species.

Claims 1, 11 and 13 are examined on the merits herein with the aforementioned elected species.

Claim Objections

Claim 13 is objected to because of the meaning of the term "hemophilia B" presented in the present application. It is noted that in the instant specification, the term "hemophilia B" refers to a disease in which Factor VIII is deficient (see at least page 6, lines 27-28; page 7, lines 25-28). However, the disease caused by the deficiency of the clotting Factor VIII is well recognized in the art as hemophilia A as evidenced by the teachings of Connelly et al. (US 5,935,935) and Couto et al. (US 6,221,349).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1. A method for providing a biologically active alpha-galactosidase A to a patient suffering from Fabry Disease, comprising administering to the lung a transgene delivery vector comprising a nucleotide sequence encoding alpha-galactosidase A, wherein said transgene delivery vector transfects lung cells, expresses the alpha-galactosidase A, and the alpha-galactosidase A enters into the patient's circulatory system; and

2. A method for providing a biologically active Factor VIII or Factor IX to a patient having deficiency in Factor VIII or Factor IX, respectively, comprising administering to the lung a transgene delivery vector comprising a nucleotide sequence encoding either Factor VIII or Factor IX, wherein said transgene delivery vector transfects lung cells, expresses the Factor VIII or Factor IX, and the Factor VIII or Factor IX enters into the patient's circulatory system;

does not reasonably provide enablement for other methods of treatment of a patient suffering from any other systemic disorder or disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

1. The breadth of the claims

The claims are directed to a method for treatment of a patient suffering from any systemic disorder or disease, including any lysosomal storage disease or any blood clotting deficiency, by administering to the lung through any route of delivery a transgene delivery vector comprising a nucleotide sequence encoding any therapeutic protein such that the transgene delivery vector transfects lung cells, expresses the therapeutic protein, and the therapeutic protein enters into the patient's circulatory system.

2. The state and unpredictability of the prior art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the present application (1/17/2000), the attainment of any therapeutic effect in any patient via gene therapy was, and remains highly unpredictable. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression and host immune manipulation is needed **to make gene therapy a reality**. Dang et al. pointed out several factors limiting an effective human gene therapy, including sub-optimal vectors,

the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells (last paragraph, col. 2, page 474). Romano et al. (Stem Cells 18:19-39, 2000) stated "The potential therapeutic applications of gene transfer technology are enormous. However, **the effectiveness of gene therapy programs is still questioned**", and "[d]espite the latest significant achievements reported in vector design, **it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame**" (see abstract, col. 2). Even in 2005, Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005) still state "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but **it has yet to deliver its promised potential**", and "[I]f scientists from many different disciplines participate and pull together as a tem to tackle the obstacles, **gene therapy will be added to our medicinal armada** and the ever-expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph). Goncalves (BioEssays 27:506-517, 2005) also states "Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph). Gardlik et al. (Med. Sci. Monit. 11:RA110-121,

2005) conclude "Although clinical trials have already started, **there are still numerous limitations that must be solved before routine clinical use**. Nevertheless, it can be expected that **future research will bring tissue- and disease-specific delivery strategies and that this hurdle will be overcome at last**" (page RA119, right-hand column, last paragraph).

3. The amount of direction or guidance provided

Apart from the exemplification showing the persistence of alpha-galactosidase A expression and reduction of GL-3 levels following intranasal administration of Ad2CMVH1αgal in Fabry mice, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain effective levels of therapeutic proteins that yield therapeutic effects for any other lysosomal storage diseases, let alone for any other systemic disorder or disease. The exemplification is not reasonable correlated to the instant broadly claimed invention in light of state and the unpredictability for attaining any therapeutic effects via gene therapy already discussed in the preceding paragraph.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

4. Working example provided

Apart from the exemplification shown in the Fabry mouse model, there is no evidence indicating that therapeutic effects have been attained or achieved for patients suffering from other systemic disorder or disease by administering to the lung a transgene delivery vector encoding for any other therapeutic protein.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the gene therapy art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Ziegler et al. (Human Gene Therapy 10:1667-1682, 1999; IDS).

Ziegler et al teaches a method for correction of enzymatic and lysosomal storage defects in Fabry mice by injecting intravenously into the Fabry mice a recombinant adenoviral vector encoding human alpha-galactosidase A (see at least the abstract). The method resulted in the detection of alpha-galactosidase A in the lung among other tissues (e.g., liver heart, spleen, kidney) at levels several logs higher than those observed in untreated Fabry mice, and 10- to 100-fold greater than those observed in wild type C57BL/6 mice (page 1670, right hand column, second paragraph; and particularly Figure 2). The detection of alpha-galactosidase A in the lung indicated that

lung cells were also transfected by the recombinant adenoviral vectors, and thereby the reference meets the limitation "administering to the lung a transgene delivery vector". Ziegler et al further teaches that alpha-galactosidase A was also detected in the plasma of treated Fabry mice (see at least Figure 6).

Accordingly, the teachings of Ziegler et al meet every limitation of the instant broad claim. Therefore, the claim is anticipated by the reference.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Yew et al. (US 6,066,626; IDS).

Yew et al teaches a method for providing a biologically active human alpha-galactosidase A to cells of an individual having deficiency in biologically active human alpha-galactosidase A or Fabry disease, said method comprising *in vivo* administration into cells competent for the production of biologically active human alpha-galacosidase A of a vector comprising and expressing a DNA sequence encoding biologically active human alpha-galactosidase A, wherein the vector is taken up by the cells competent for the production of biologically active human alpha-galactosidase A, the DNA sequence is expressed therein and biologically active human alpha-galactosidase is produced (see at least the abstract and claims 1-14). Yew et al further teaches the *in vivo* administration includes intranasal instillation into the lung and intravenous administration, and that both of these routes of administration result in the expression of the recombinant alpha-galactosidase A in lung cells and other tissues (col. 11, lines 14-33; see examples and at least Figures 5-6). Yew et al also teaches that the

recombinant alpha-galactosidase A is secreted and it is captured by distant cells though the mannose-6-phosphate receptors (col. 11, lines 34-47).

Accordingly, the teachings of Yew et al meet every limitation of the instant broad claim. Therefore, the claim is anticipated by the reference.

Claims 1, 11 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Connelly et al. (US 5,935,935) as evidenced by Ziegler et al. (Human Gene Therapy 10:1667-1682, 1999; IDS).

Connelly et al teaches the production of high titer, stable, adenoviral vectors that produce therapeutic levels of clotting factors, specifically Factor VIII and Factor IX, *in vivo* and a method for treating patients with hemophilia A and hemophilia B, using recombinant adenoviral vectors expressing Factor VIII and Factor IX, respectively (col. 1, lines 15-28; col. 4, lines 1-6; and at least claim 54). Connelly et al teaches specifically that the recombinant adenoviral vectors can be administered by intravenously and intranasally among other routes of delivery (col. 11, lines 1-5). Intranasal administration of the recombinant adenoviral vectors would result in the transfection of lung cells, and that intravenous delivery of the recombinant adenoviral vectors has been shown to result in the transfection of lung cells as evidenced by the teachings of Ziegler et al. (Human Gene Therapy 10:1667-1682, 1999; IDS). Persistent high expression levels of both human Factor VIII and IX were detected in plasma (see examples).

As noted previously, the term "hemophilia B" in the present application refers unconventionally to a disease having a deficiency in Factor VIII (see at least page 6, lines 27-28; page 7, lines 25-28). Accordingly, the teachings of Connelly et al meet every limitation of the instant broad claims. Therefore, the claims are anticipated by the reference.

Claims 1, 11 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Couto et al. (US 6,221,349).

Couto et al provides improved AAV vectors and methods for treating hemophilia A by delivering nucleic acids coding for the clotting Factor VIII to a mammal (e.g., a hemophilia A patient) under conditions that result in the expression of Factor VII protein at a level that provides a therapeutic effect such as decreasing the time for the mammal's blood to clot (see at least Summary of the Invention; col. 1; lines 19-47; col. 12, lines 1-8; and the claims). Couto et al further teaches that the recombinant AAV vectors can be administered nasally or by pulmonary administration among many other routes of deliveries (col. 18, line 59 continues to line 5 of col. 19). The methods taught by Couto et al would result in the transfection of lung cells with the recombinant AAV expressing Factor VIII, and that the recombinant Factor VIII would enter into the patient's circulatory system to yield the desired therapeutic effect such as decreasing the time for the mammal's blood to clot.

As noted previously, the term "hemophilia B" in the present application refers unconventionally to a disease having a deficiency in Factor VIII (see at least page 6,

lines 27-28; page 7, lines 25-28). Accordingly, the teachings of Couto et al meet every limitation of the instant broad claims. Therefore, the claims are anticipated by the reference.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,066,626.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claim is directed to a method for treatment of a patient suffereing from a systemic disorder or disease, comprising administering to the lung a transgene delivery vector, said transgene delivery vector comprising a nucleotide

sequence which encodes for a therapeutic protein, such that the transgene delivery vector transfects lung cells, expresses the therapeutic protein, and the therapeutic protein enters into the patient's circulatory system; whereas claims 1-14 of U.S. Patent No. 6,066,626 are drawn to methods for providing a biologically active human alpha-galactosidase A to cells of an individual having deficiency in biologically active human alpha-galactosidase A or Fabry disease, said method comprising *in vivo* administration into cells competent for the production of biologically active human alpha-galacosidase A of a vector comprising and expressing a DNA sequence encoding biologically active human alpha-galactosidase A, wherein the vector is taken up by the cells competent for the production of biologically active human alpha-galactosidase A, the DNA sequence is expressed therein and biologically active human alpha-galactosidase is produced.

The claim of the present application differ from the claims of the U.S. Patent No. 6,566,581 in reciting specifically administering to the lung a transgene delivery vector such that the transgene delivery vector transfects lung cells, expresses the encoded therapeutic protein and the therapeutic protein enters the circulatory system of the treated patient. The claim of the present application can not be considered to be patentably distinct over claims 1-14 of U.S. Patent No. 6,066,626 when there is a specific disclosed embodiment of the issued US patent that teaches *in vivo* administration includes intranasal instillation into the lung and intravenous administration, and that both of these routes of administration result in the expression and secretion of the recombinant alpha-galactosidase A in lung cells (col. 11, lines 14-33).

Accordingly, the claims of issued U.S. Patent No. 6066,626 fall within the scope of the broad claim 1 of the present application.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D
PATENT EXAMINER